Statistical Analysis Plan for Study M21-323

Phase 3, Multicenter Open-label Extension Study to Evaluate the Safety of BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex for the Treatment of Platysma Prominence

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Version 3.0

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1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for BOTOX (Botulinum Toxin Type A) for Study M21-323, entitled "Phase 3, Multicenter Open-label Extension Study to Evaluate the Safety of BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex for the Treatment of Platysma Prominence."

Study M21-323 examines the long-term safety of repeated BOTOX (Botulinum Toxin Type A) treatments of platysma prominence in subjects who have previously completed a lead-in pivotal Phase 3 study. The SAP will not be updated in case of administrative changes or amendments to the protocol unless the changes impact the analysis.

Unless noted otherwise, all analyses will be performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC 27513) or later under the Linux operating system.

2.0 Study Design and Objectives

2.1 Objectives, Hypotheses and Estimands

The study objective is to evaluate the long-term safety of repeat treatments of BOTOX in subjects with moderate to severe platysma prominence at maximum contraction.

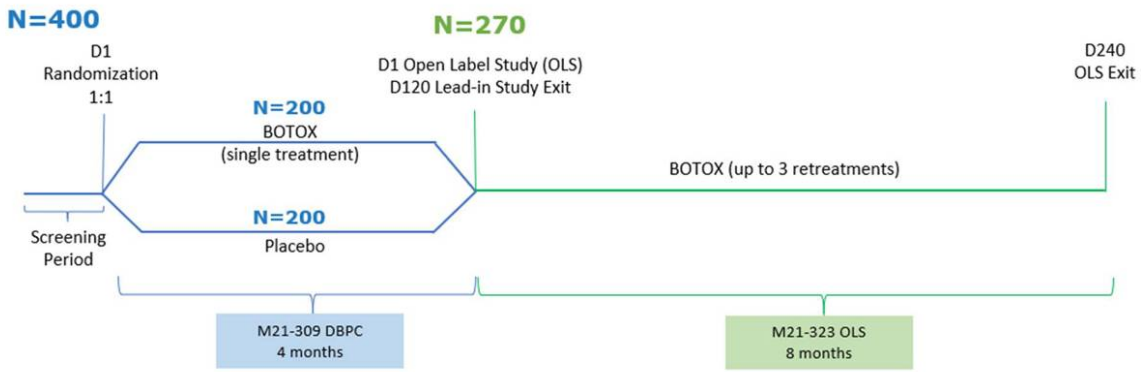
The clinical hypothesis is that BOTOX is a safe treatment after repeat treatment in adult subjects with moderate and severe platysma prominence.

As the objective is to evaluate safety, no formal testing will be conducted and no estimands are provided.

2.2 Study Design Overview

The schematic is shown in Figure 1 with the current M21-323 open-label study (OLS) as an extension of the M21-309 double-blind placebo-controlled (DBPC) lead-in study.

Figure 1. Study Schematic



2.3 Treatment Assignment and Blinding

This study is an open-label study with no control group and no randomization. Study drug (BOTOX) will be unblinded.

2.4 Sample Size Determination

No formal statistical power or sample size calculation was performed for this study. Approximately 270 subjects are anticipated to be enrolled or rolled-over into this study.

[redacted]

3.0 Endpoints

3.1 Primary Endpoint

For both US FDA and European Union (EU) regulatory agencies, the primary endpoint of the study is incidence of adverse events.

3.2 Secondary Endpoint

Not applicable.

3.3 Other Efficacy Endpoints

[redacted]

3.4 Safety Endpoints

The primary endpoint is the incidence of adverse events (AEs). Safety parameters include AEs and vital signs. Safety analyses will be performed by study drug group (e.g., lead-in study treatment, along with BOTOX treatments in this study) and number of BOTOX cycles (i.e., total number of treatment cycles up to 4, including BOTOX treatment from the lead-in study).

3.5 Additional Endpoint(s)

Not applicable.

4.0 Analysis Populations

The following population sets will be used for the analyses.

For US FDA analyses, efficacy variables will be analyzed based on the intent-to-treat (ITT) population. The ITT population consists of all subjects who enrolled in this study.

For EU regulatory agencies only, the efficacy analyses will be performed on the modified intent-to-treat (mITT) population, [redacted]

Safety analyses will be based on the Safety Analysis Set (safety population), which consists of all subjects who received at least 1 dose of study drug either in the lead-in study or in this study. Subjects will be analyzed by actual study drug received, including both the lead-in study, as well as during this study.

Subject data from the current study will be integrated with the corresponding subject data from the lead-in study.

5.0 Subject Disposition

The total number of subjects who were enrolled and treated will be summarized.

A summary of subject accountability will be provided where the number of subjects in each of the following categories will be summarized for each treatment group (including from the lead-in study):

- Subjects enrolled in the study;
- Subjects who took at least one dose of study drug;
- Subjects who completed the study;
- Subjects who prematurely discontinued study drug;
- Subjects in each analysis population, as applicable.

For end of study participation, the number and percentage of subjects who completed the protocol defined follow-up period will be summarized overall and by treatment group and treatment cycles.

6.0 Study Drug Duration

For the safety population, the number of subjects treated will be presented by treatment received for the lead-in study and for this study, as well as by number of cycles within this study. If a subject does not receive the full dose, this will be indicated; significant deviations to dosing will be reported.

7.0 Demographics, Baseline Characteristics, Medical History, and Prior/Concomitant Medications

Demographics, baseline and disease characteristics, medical history, and prior and concomitant medications will be summarized for the ITT and mITT populations overall and by treatment group (including lead-in study) based on the lead-in study baseline data.

Categorical variables will be summarized with the number and percentage of subjects; percentages will be calculated based on the number of non-missing observations.

Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean and standard deviation, median, minimum and maximum).

7.1 Demographics and Baseline Characteristics

Continuous demographic variables include age, weight, height, and body mass index (BMI). Categorical demographic and baseline variables include sex, ethnicity, race, age group [redacted] C-APPS grade, P-APPS grade, Fitzpatrick Skin Phototype, BAS-PP Items 1 and 2, ANLFQ-Satisfaction (Baseline) Item 5, and ANLFQ-Impacts domain based on the lead-in study data.

7.2 Medical History and Prior and Concurrent Procedures

Medical history data will be reported and summarized separately from prior procedures data for the ITT and mITT populations. Medical history data and prior procedure data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The actual

version of the MedDRA coding dictionary will be noted in the statistical tables and clinical study report. The number and percentage of subjects in each medical history category (by MedDRA system organ class and preferred term) will be summarized overall and by treatment group. The system organ class (SOC) will be presented in alphabetical order, and the preferred terms will be presented in alphabetical order within each SOC. Subjects reporting more than one condition/diagnosis will be counted only once in each row (SOC or preferred term). Similarly, the number and percentage of subjects in each prior procedure category will be summarized overall and by treatment group by MedDRA high level term and preferred term.

In addition, any concurrent procedures, defined as any procedure performed on or after the date of first treatment in this study, will be summarized by MedDRA high level term and PT in each treatment group for the ITT and mITT populations.

7.3 Prior and Concomitant Medications

Prior and concomitant medications will be summarized by generic name for the ITT and mITT populations. A prior medication is defined as any medication taken prior to the date of the first dose of study drug in this study. A concomitant medication is defined as any medication that started prior to the date of the first dose of study drug in this study and continued to be taken after the first dose of study drug or any medication that started on or after the date of the dose of study drug, but not after the date of the last visit assessment. The number and percentage of subjects taking medications will be summarized by generic drug name based on the World Health Organization (WHO) Drug Dictionary for both prior and concomitant medications.

8.0 Handling of Potential Intercurrent Events for the Primary and Key Secondary Endpoints

For the primary endpoint, AEs will be reported as observed, without additional handling of potential intercurrent events.

There are no secondary endpoints in this study.

9.0 Efficacy Analyses

9.1 General Considerations

Summary and Analysis of the Primary Endpoint

There are no primary efficacy endpoints. The primary endpoint is safety, and the analyses related to the primary endpoint of incidence of AEs are described in Section 10.0.

Summary and Analysis of Efficacy Endpoints

In general, the proportions of subjects who achieve the efficacy endpoints will be summarized with frequency tables. The 95% confidence intervals for response will be estimated based on the observed data by study drug group and by BOTOX treatment cycle (both lead-in study as well as this study). No missing data imputation or statistical testing will be performed.

For the US FDA, efficacy measures will be summarized using descriptive statistics using the ITT population based on the observed data. For the EU efficacy measures, descriptive statistics will be reported for the mITT population based on observed data. Continuous measures will be reported by timepoint using the number observed, mean, standard deviation, median, 25th and 75th quartiles, minimum and maximum. Categorical measures will be reported by time point using the number observed, counts for each category, and percentages. In addition, for the responder definitions, the 95% CIs will be included.

[redacted]

9.2 Handling of Missing Data

In general, no missing data will be imputed for the efficacy analyses. If a score (C-APPS or P-APPS) is missing for one side, then the average will be based on the score of the other side (see Section 9.1). If both scores are missing for both sides, then the score will be missing.

9.3 Primary Efficacy Endpoint and Analyses

9.3.1 Primary Efficacy Endpoint

There is no primary efficacy endpoint. The primary endpoint is incidence of AEs (safety).

9.3.2 Main Analysis of Primary Efficacy Endpoint

Not applicable.

9.3.3 Sensitivity and Supplementary Analyses of the Primary Efficacy Endpoint

Not applicable.

9.4 Secondary Efficacy Endpoints and Analyses

9.4.1 Key Secondary Efficacy Endpoints

Not applicable.

9.4.2 Main Analyses of Key Secondary Efficacy Endpoints

Not applicable.

9.4.3 Sensitivity and Supplementary Analyses for Key Secondary Efficacy Endpoints

Not applicable.

9.4.4 Supportive Secondary Efficacy Endpoints and Analyses

Not applicable.

9.5 Efficacy Endpoints and Analyses

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.6 Efficacy Subgroup Analyses

Not applicable.

10.0 Safety Analyses

10.1 General Considerations

Safety data will be summarized for the Safety Analysis Set. For the safety analysis, subjects are assigned to a treatment group based on the treatment actually received and will be presented by treatment groups and by treatment cycle, including number of BOTOX treatment cycles (up to 4, including the lead-in study). Safety analyses will take into account both study drug groups and number of BOTOX treatment cycles (e.g., placebo or BOTOX in the lead-in Phase 3 study, BOTOX in this study up to 3 treatment cycles) from both the lead-in Phase 3 study and this study.

The safety parameters will include incidence of AEs and change from lead-in study baseline in vital signs. For each safety parameter evaluating change from lead-in study baseline, the last nonmissing safety assessment before study drug administration of the lead-in study will be used as baseline for all analyses of that parameter.

10.2 Adverse Events

Adverse events (AEs) will be summarized and presented using primary MedDRA System Organ Classes (SOCs) and preferred terms (PTs) according to the version of the MedDRA coding dictionary used for the study at the time of database lock. The actual version of the MedDRA coding dictionary used will be noted in the AE tables and in the clinical study report. Specific adverse events will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs

multiple times within a subject, the highest severity and level of relationship to investigational product will be reported.

10.2.1 Treatment-Emergent Adverse Events

Treatment-emergent AEs (TEAEs) are defined as any AE with the onset that is after the first dose of study drug. For the lead-in study, the TEAEs will already be defined, and will be counted in the overall group presentation of events. TEAEs collected for this study will be counted as TEAEs of the previous study if the first dose of study drug was not administered in this study; otherwise, they will be counted as TEAEs in this study after the first dose of study drug in this study. Events where the onset date is the same as the study drug start date are assumed to be treatment-emergent. All TEAEs will be summarized overall, as well as by primary MedDRA SOC and PT. The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC.

The number and percentage of subjects experiencing treatment-emergent AEs will be summarized.

10.2.2 Adverse Event Overview

An overview of AEs will be presented consisting of the number and percentage of subjects experiencing at least one event for each of the following AE categories:

- Any TEAE
- Any TEAE related to study treatment
  - Any TEAE related to study drug according to the investigator
  - Any TEAE related to study procedure according to the investigator
- Any mild TEAE
  - Any mild TEAE related to study treatment according to the investigator
- Any moderate TEAE
  - Any moderate TEAE related to study treatment according to the investigator

- Any severe TEAE
  - Any severe TEAE related to study treatment according to the investigator
- Any serious TEAE
  - Any serious TEAE related to study treatment according to the investigator
- Any TEAE leading to death
- Any TEAE leading to discontinuation of study treatment
- Any treatment-emergent adverse event of special interest (AESI)
- Any possible distant spread of toxin (PDSOT) TEAE
- All deaths

10.2.3 Treatment-Emergent Adverse Events by SOC and/or PT

Treatment-emergent adverse events will be summarized by SOC and PT; by maximum relationship to study drug as assessed by the investigator (e.g., reasonable possibility or no reasonable possibility) and SOC and PT; by maximum severity and SOC and PT; and by subject number and SOC and PT. Specific adverse events will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times within a subject, the highest severity and level of relationship to investigational product will be reported.

In addition, treatment-emergent adverse events will be summarized by PT and sorted by decreasing frequency for the total active group.

10.2.4 Treatment-Emergent Adverse Events per Patient-Years of Exposure

Not applicable.

10.2.5 SAEs (Including Deaths) and Adverse Events Leading to Study Drug Discontinuation

SAEs (including deaths) and AEs leading to study drug discontinuation will be summarized by SOC and PT and in listing format.

10.2.6 Adverse Events of Special Interest and Possible Distant Spread of Toxin Adverse Events

Treatment-emergent adverse events of special interest (AESIs) will be summarized by PT. [redacted]

Possible distant spread of toxin (PDSOT) AEs will be summarized by PT. [redacted]

Tabular listings of AESIs and PDSOT AEs will be provided.

10.3 Analysis of Laboratory Data

Not applicable.

10.4 Analysis of Vital Signs

Vital sign measurements of systolic and diastolic blood pressure, pulse rate, and respiratory rate, and changes from lead-in study baseline at each assessment timepoint will be summarized by treatment group. In addition, potentially clinically important vital sign values will be summarized.

[redacted]

10.5 Safety Subgroup Analyses

[redacted]

10.6 Other Safety Analyses

Not applicable.

11.0 Other Analyses

Not applicable.

12.0 Interim Analyses

No interim analysis is planned for this study.

12.1 Data Monitoring Committee

No data monitoring committee (DMC) will be used for this study.

13.0 Overall Type-I Error Control

Not applicable for this study. No formal testing will be done. All data will be presented without hypothesis testing.

14.0 Version History

Table 2. SAP Version History Summary

Version	Date	Summary
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

15.0 References

Not applicable.

Appendix A. Protocol Deviations

The number and percentage of subjects who reported at least one of the following protocol deviation categories will be provided.

- Subject entered into the study even though did not satisfy entry criteria.
- Subject developed withdrawal criteria during the study and was not withdrawn.
- Subject received wrong treatment or incorrect dose for study treatment.
- Subject received prohibited concomitant medication or procedure.